

Efavirenz (Sustiva)

Summary

Efavirenz is a type of anti-HIV drug from a class of drugs commonly called non-nukes. Efavirenz is used as part of combination therapy for people with HIV. The most common side effects of efavirenz include dizziness, difficulty falling asleep, trouble concentrating and rash. Dosage of efavirenz depends on which other drugs are part of your anti-HIV therapy.

What is efavirenz?

Efavirenz, sold under the brand name Sustiva in Canada and the United States (Stocrin in Europe and many other parts of the world) and also in Atripla, is a type of anti-HIV drug (antiretroviral) called non-nuke or NNRTI (non-nucleoside reverse transcriptase inhibitor). Efavirenz is used in combination with other anti-HIV drugs to treat HIV.

How does efavirenz work?

When HIV infects a cell, it takes control of that cell. HIV then forces the cell to make many more copies of the virus. To make these copies, the cell uses proteins called enzymes. When the activity of these enzymes is reduced the production of HIV slows.

Efavirenz belongs to a group or class of drugs called non-nucleoside reverse transcriptase inhibitors. Efavirenz interferes with an enzyme called reverse transcriptase (RT), which is used by HIV-infected cells to make new viruses. Since efavirenz inhibits, or reduces, the activity of this enzyme, this drug causes HIV-infected cells to produce fewer viruses.

How do people with HIV use efavirenz?

Efavirenz is used in combination with several other anti-HIV drugs, usually nukes (nucleoside analogues), and sometimes drugs from other classes such as protease inhibitors. Such combinations are called antiretroviral therapy, or ART. For more information on ART, see CATIE's *Your Guide to HIV Treatment*.

For many people with HIV, the use of ART has increased their CD4 cell counts and decreased the amount of HIV in their blood (viral load). These beneficial effects help to reduce the risk of developing a life-threatening infection.

FACT SHEET

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Neither efavirenz nor any other anti-HIV medication is a cure for HIV. It is therefore important that you do the following:

- See your doctor regularly so that he or she can monitor your health.
- Continue to practise safer sex and take other precautions to prevent passing HIV on to other people.

Warnings

1. Suicide risk

In a review of several studies comparing 3,241 efavirenz users with 2,091 non-users, researchers found that in a small proportion of people, about 2%, there was an increased risk of suicide-related behaviour among people who used efavirenz. These behaviours included the following:

- thoughts of suicide
- attempts at suicide
- completed suicide

This elevated risk of suicide-related behaviour was double that seen in people who did not use efavirenz.

Before you start therapy with efavirenz: let your doctor know right away if you have ever had any of the following:

- thoughts of, or attempted suicide
- use street or club drugs
- anxiety or excess worry
- suffered from depression
- bipolar disorder
- difficulty falling asleep or staying asleep

Tell your doctor how much and how often you drink alcohol.

After you start therapy with efavirenz: if you have thoughts of suicide or harming yourself while taking efavirenz, contact your doctor immediately or call emergency services by telephoning 911.

2. Mental health

Some people who use efavirenz may experience problems with thoughts and feelings. For example, you may:

- become easily upset or angry
- have unexpected feelings of sadness
- have prolonged feelings of sadness, anger or depression
- feel hopeless
- have loss of pleasure in everyday activities
- feel fearful
- unexpectedly feel tired or experience a lack of energy
- have difficulty falling asleep, staying asleep or waking up prematurely
- have strange thoughts
- have thoughts about harming yourself or others
- have thoughts about suicide

If you notice any of these problems before or after you have started to take efavirenz, talk to your doctor right away.

3. Pregnancy

Leading U.S. treatment guidelines recommend that prior to starting efavirenz, women should have a pregnancy test. Then the guidelines recommend that these women should be counselled about the risk of efavirenz on the health of the fetus and that it is best to not become pregnant while taking efavirenz.

If you are a woman who is pregnant or wants to have a baby and you are taking efavirenz, let your doctor know right away. Efavirenz has caused birth defects in pregnant monkeys. Efavirenz may weaken the effectiveness of hormonal contraceptives—such as the “pill,” implants or injections. The manufacturer suggests that women use barrier methods, such as condoms, to prevent pregnancy if they are taking efavirenz.

4. Abnormal heart rhythms

Efavirenz can cause abnormal heart rhythms. Symptoms related to this can include feeling faint or fainting, or seizures. If you or a close relative (mother, father, sister, brother) have a history of heart problems including abnormal heart rhythms, let your doctor know right away.

5. Marijuana testing

In some cases, people taking efavirenz may falsely test positive for marijuana in drug screening assays or tests. These tests detect chemicals found in marijuana, which are released into urine. According to the manufacturer of efavirenz, a confirmatory test (using gas chromatography) will clear up the matter by revealing the presence of efavirenz and not chemicals found in marijuana. This information may be useful to people taking efavirenz who have to undergo drug testing for various reasons.

6. Hepatitis and liver health

The manufacturer recommends that efavirenz should **not** be used by people with moderate or severe liver damage.

7. Different strains of HIV

There are many strains or subtypes (also called clades) of HIV, such as A, B and E. Clade B HIV is most commonly found in North America and Western Europe. However, due to travel and immigration, other clades of HIV can also be found in these regions. Efavirenz is effective against many different types of non-B clades of HIV. However, laboratory tests have found that efavirenz is not as effective against strains of HIV called "group O." For more information about the strain of HIV that you have, speak to your doctor.

Side effects

1. Central nervous system

The most common side effects from efavirenz affect the central nervous system (CNS), and include the following:

- dizziness
- difficulty falling asleep
- difficulty concentrating
- feeling drowsy during the daytime

Less common CNS side effects include:

- vivid dreams (these may be pleasant or unpleasant)
- hallucinations

CNS side effects, which affect at least half of people living with HIV who use efavirenz, usually appear on the first or second day of therapy. Common CNS side effects—dizziness, difficulty falling asleep, drowsiness, decreased concentration—should begin to fade within the first month of taking efavirenz. Some doctors suggest taking efavirenz in the morning or in the early evening to reduce its impact on your ability to fall asleep. If you are having difficulty coping with these or any other side effects, let your doctor know right away. Use of alcohol and street or club drugs may make efavirenz's CNS side effects worse.

In rare cases efavirenz may cause seizures. If you have a history of seizures let your doctor know before you start taking efavirenz.

2. Rash

As with all non-nukes, efavirenz can cause some users to develop a rash. The rash usually occurs during the second week of therapy. Let your doctor know right away if this happens. A rash associated with efavirenz is usually not severe and goes away after about two weeks without special treatment. Your doctor may prescribe medication, such as antihistamines, to help ease the irritation of the rash.

In rare cases, the rash may become severe and other symptoms may occur, such as blisters on the skin, itchy eyes, swelling, and muscle or joint pain. If this happens, call your doctor immediately.

3. Liver enzymes

Increased levels of liver enzymes have been reported in some efavirenz users. In some cases, this may be an indicator of liver damage.

4. Lipodystrophy syndrome

In 2007 two clinical trials in the U.S. suggested that the use of efavirenz is associated with a significantly increased risk for changes in body shape. Efavirenz use is also linked to an increased level of cholesterol in the blood. These changes are part of a larger set of changes known as the lipodystrophy syndrome.

The HIV lipodystrophy syndrome is the name given to a range of symptoms that can develop over time when people use ART regimens. Some features of lipodystrophy syndrome include:

- loss of fat just under the skin (subcutaneous fat) in the face, arms and legs
- bulging veins in the arms and/or legs due to the loss of fat under the skin
- increased waist and belly size
- fat pads at the back of the neck (“buffalo hump”) or at the base of the neck (“horse collar”)
- small lumps of fat in the abdomen
- increased breast size (in women)

Together with these physical changes, blood tests may detect the following:

- increased levels of fatty substances called triglycerides
- increased levels of LDL cholesterol (low-density lipoprotein), or “bad” cholesterol
- increased levels of sugar (glucose)
- increased levels of the hormone insulin

- decreased sensitivity to insulin (insulin resistance)
- decreased levels of HDL cholesterol (high-density lipoprotein), or “good” cholesterol

The precise causes of the HIV lipodystrophy syndrome are not clear and are difficult to understand because some people living with HIV may experience one or more aspects of the syndrome. For instance, some people may experience fat wasting, others fat gain, and others may experience both fat wasting and gain. What is becoming increasingly clear is that unfavourable changes in the levels of glucose, cholesterol and triglycerides over a period of several years increase the risk of diabetes and cardiovascular disease. So far, however, the many benefits of ART far outweigh the increased risk of cardiovascular disease or other side effects.

Maintaining a normal weight, eating a healthy diet, exercising regularly and quitting smoking are all important to help you to reduce your risk of diabetes, heart disease and other complications. Regular visits to your doctor for checkups and blood tests are a vital part of staying healthy. If necessary, your doctor can prescribe lipid-lowering therapy.

Researchers are studying the lipodystrophy syndrome to try to discover ways of helping people with HIV avoid or reduce this problem. To find out more about options for managing aspects of the lipodystrophy syndrome, see *CATIE's Practical Guide to HIV Drug Side Effects*.

5. Breast enlargement in males

Temporary breast enlargement has been reported by a small proportion of men using ART regimens, including some that took efavirenz. Generally, this problem cleared when the men stopped taking efavirenz.

Breast enlargement has also been reported by other men who used ART regimens without efavirenz. This problem can occur in men, particularly under the following conditions:

- having less-than-normal levels of testosterone
- use of drugs that impair the production or activity of testosterone—ketoconazole

(Nizoral), metronidazole (Flagyl), cimetidine (Tagamet), flutamide (Euflex)

- use of growth hormone
- having higher-than-normal levels of thyroid hormones (hyperthyroidism)
- use of street drugs—marijuana, heroin
- the presence of liver disease

If breast enlargement does occur while you are taking ART, speak to your doctor about this as there may be several options for managing this condition.

6. Bone health

Taking efavirenz may reduce levels of vitamin D in your body. Vitamin D is needed to absorb calcium and to help strengthen bones.

When some HIV-positive people initiate ART, the density of their bones decreases. The decrease in bone density tends to stabilize within one or two years after starting ART. It may be useful for you to discuss with your doctor the possibility of having bone density assessments done before you begin taking ART. If your bones are thin, talk to your doctor about your intake of calcium and vitamin D₃. Regular monitoring of your bone density may also be useful.

For more information about vitamin D and bones, see CATIE's *Practical Guide to Nutrition for People Living with HIV*.

Drug interactions

Always consult your doctor and pharmacist about taking any other prescription or non-prescription medication, including herbs, supplements and street drugs.

Some drugs can interact with efavirenz, increasing or decreasing its levels in your body. Increased drug levels can cause you to experience side effects or make pre-existing side effects worse. On the other hand, if drug levels become too low, HIV can develop resistance and your future treatment options may be reduced.

It may also be necessary to avoid drugs that do not affect efavirenz drug levels, but cause similar side effects.

If you must take a drug that has the potential to interact with your existing medications, your doctor can do the following:

- adjust the dose of either your anti-HIV drugs or other medications; or
- prescribe different anti-HIV drugs for you.

The following drugs interact or have the potential to interact with efavirenz. These lists are not exhaustive.

The manufacturer recommends that the following drugs should not be taken by people using efavirenz because this could lead to serious (even life-threatening) interactions.

- antihistamines—astemizole (Hismanal)
- anti-migraine (ergot derivatives)—dihydroergotamine (Migranal), ergotamine (Ergomar), Ergonovine
- benzodiazepines—midazolam (Versed), triazolam (Halcion)
- gastrointestinal motility drugs—cisapride (Prepulsid)
- antifungal drugs—voriconazole (Vfend), posaconazole (Posanol)
- antipsychotics—pimozide (Orap)

The following drugs can *increase* levels of efavirenz in your body:

- anti-HIV drugs—ritonavir (Norvir)

The following drugs can *decrease* levels of efavirenz in the blood:

- antibiotics/anti-tuberculosis drugs—rifampicin
- herbs—St. John's wort, Ginkgo biloba

Efavirenz can *decrease* levels of the following drugs:

- antibiotics—clarithromycin (Biaxin)
- anti-tuberculosis drugs—rifabutin (Mycobutin)
- antidepressants—sertraline (Zoloft)

- antifungal drugs—itraconazole (Sporanox), ketoconazole (Nizoral)
- anti-HIV drugs—amprenavir (Agenerase), fosamprenavir (Telzir), indinavir (Crixivan), lopinavir (in Kaletra), ritonavir (Norvir), and saquinavir (Invirase; when saquinavir is used as the only protease inhibitor in a regimen)
- anti-seizure drugs—carbamazepine (Tegretol), phenytoin (Dilantin), phenobarbital
- narcotics—methadone (your dose of methadone may need to be increased if you use efavirenz)
- transplant drugs—efavirenz can reduce the concentration of commonly used transplant medicines in your blood. Examples of these medicines include cyclosporine (Neoral, Sandimmune), sirolimus (Rapamune) and tacrolimus (Prograf)

Resistance, cross-resistance and treatment interruption

Over time, as new copies of HIV are made in the body, the virus changes its structure. These changes, called mutations, can cause HIV to resist the effects of anti-HIV drugs, which means those drugs will no longer work for you. Combining efavirenz with at least two other anti-HIV drugs delays the development of drug resistance.

To reduce the risk of developing drug resistance, all anti-HIV drugs should be taken every day exactly as prescribed and directed. If doses are delayed, missed or not taken as prescribed, levels of efavirenz in the blood may fall too low. If this happens, resistant virus can develop. If you find you are having problems taking your medications as directed, speak to your doctor and nurse about this. They can find ways to help you.

When HIV becomes resistant to one drug in a class, it sometimes becomes resistant to other drugs in that class. This is called cross-resistance. Feel free to talk with your doctor about your current and future treatment options. To help you decide what these future therapies might be, at some point your doctor can have a small sample of your blood analyzed using resistance testing. Should HIV in

your body become resistant to efavirenz, your doctor, with the help of resistance testing, can help put together a new treatment regimen for you.

If you stop taking efavirenz, low levels of this drug can remain in your body for up to three weeks. In the absence of combination therapy, these low levels of efavirenz are not high enough to suppress HIV and can lead to the development of HIV that is resistant to efavirenz. Therefore, if you are taking efavirenz and need to interrupt your therapy, speak to your specialist about ways to minimize the chance that HIV in your body might become resistant to efavirenz. HIV that is resistant to efavirenz is also usually resistant to other NNRTIs, such as rilpivirine (Edurant), nevirapine (Viramune) and delavirdine (Rescriptor).

Dosage and formulations

Efavirenz is available as 600 mg tablets and 50 mg, 100 mg and 200 mg capsules. Take efavirenz with water. Do not chew the capsules or tablets.

Availability

Efavirenz is licensed in Canada for the treatment of HIV infection in adults, in combination with other anti-HIV drugs. Your doctor can tell you more about the availability and coverage of efavirenz in your region. CATIE's online module *Federal, Provincial and Territorial Drug Access Programs* also contains information about Canadian drug coverage.

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Disclaimer

Decisions about particular medical treatments should always be made in consultation with a qualified medical practitioner knowledgeable about HIV- and hepatitis C-related illness and the treatments in question.

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